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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,909	10/29/2003	James B. Lorens	7946-79836-01	9257

74839 7590 12/11/2008

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EXAMINER	
REDDIG, PETER J	
ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
12/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/696,909	LORENS ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 23 September 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *23 September 2008*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1, 12, 14-18, 27, 41-44 and 54-61*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Karen A Canella/
Primary Examiner, Art Unit 1643

Continuation of 5. Applicant's reply has overcome the following rejection(s): The rejection of Claims 1, 12, 14-18, 27, 41-44 and 55-61 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, set forth in section 4 of the Office Action 6/23/2008 and the rejection of claims 1, 12, and 14-18 under 35 U.S.C. 112, second paragraph, set forth in section 5 of the Office Action of 6/23/208..

Continuation of 11. does NOT place the application in condition for allowance because: Claims 1, 14, 27, 54-56 and 61 remain rejected under 35 U.S.C. 102(b) as being anticipated by Healy et al. (Am. J. of Physiology, Lung Cell Molecular Physiology, June, 2001 280: L1273-L1281, previously cited).

Applicants argue that the Office alleges that Healy et al. teach "determining the in vitro kinase activity of an Axl polypeptide... [,] performing a cell-based assay in an endothelial cell.., and determining the effect of this interaction on cell number..." as well as teaching assaying apoptosis in endothelial cells expressing Axl (Office action, page 10, second paragraph). The Office further asserts that as Healy allegedly "comprises the same method steps as claimed in the instant invention, determining in vitro kinase activity of an Axl polypeptide...; and performing a cell based assay in an endothelial cell comprising said Axl polypeptide.., the claimed method is anticipated because the method will inherently be a method for identifying a compound that inhibits angiogenesis..." (Office action, paragraph bridging pages 10-11, emphasis added).

Applicants argue that a rejection under 35 U.S.C. § 102 is appropriate "only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference." MPEP § 2131. However, "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic ... Inherency, however, may not be established by probabilities or possibilities." MPEP § 2112. In order to show inherency, a gap in a reference may be filled by extrinsic evidence, but the "evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991); MPEP § 2131.01, emphasis added. Applicants strongly assert that Healy et al. does not inherently anticipate the claimed methods and the Office has not provided any extrinsic evidence to make clear that Healy et al. necessarily does so.

Applicants argue that as a preliminary matter, Applicants point out that Healy et al. teach that contacting human pulmonary artery endothelial cells (HPAEC), which express Axl polypeptide, with exogenous Gas 6 (an Axl ligand) increased Axl phosphorylation (page L1276, column 2 and Figure 5). Healy et al. also teach that contacting the HPAEC cells with Gas 6 increased cell number (page L1276, column 2 and Figure 6). Finally, Healy et al. teach that contacting the HPAEC cells, or HPAEC cells overexpressing Axl, with Gas 6 decreased apoptosis of the cells in serum free medium (page L1277, column 2; page 1278, column 2; Figures 8 and 10).

Applicants argue that Healy et al. do not teach that Gas 6 is an angiogenesis inhibitor. This has been previously noted by Applicants (Office action response of February 23, 2007, page 15, third paragraph). This has also been admitted by the Office, which stated "Healy does not teach that Gas 6 specifically inhibits angiogenesis..." (Office action of May 7, 2007, page 11, third paragraph), when this rejection was last withdrawn. In the Office action of May 7, 2007, the Office attempted to cure the deficiencies of Healy et al. by asserting that Gallicchio et al. (Blood 105:1970-1976, 2005; cited in the Office action of May 7, 2007) provides evidence that Gas 6 inhibits angiogenesis upon interacting with Axl (Office action of May 7, 2007, page 12, first paragraph).

Applicants argue that Healy et al. teach determining only the effect of Gas 6 on Axl polypeptide kinase activity and cell proliferation and apoptosis of cells expressing Axl polypeptide. Gas 6 stimulates Axl polypeptide activity, which inhibits activation of vascular endothelial growth factor receptor 2 (VEGFR2) and leads to inhibition of an angiogenic program in vascular endothelial cells (Gallicchio et al., abstract; page 1973, first full paragraph; Figure 4A). Based on Gallicchio et al., one of skill in the art would predict that inhibition of Axl polypeptide activity would stimulate activation of an angiogenic program in vascular endothelial cells. Thus, the expected effect of Healy et al. would be the opposite of Applicants' demonstrated inhibition of angiogenesis. As Gas 6 is neither an inhibitor of Axl nor an inhibitor of angiogenesis, Healy et al. do not expressly or inherently teach a method of identifying a compound that is an inhibitor of angiogenesis and therefore this reference does not anticipate the claims.

Applicants point out that the foregoing discussion was previously presented in the amendment of October 5, 2007 and it was tacitly acknowledged and accepted as persuasive by the Office, which withdrew this rejection without comment in the Office action of December 12, 2007. Applicants emphasize that this rejection under 35 U.S.C. § 102(b) has previously been overcome and that Healy et al. still does not anticipate the claims.

Applicants arguments have been considered, but have not been found persuasive. In response to applicant's arguments, the recitation of identifying a compound that inhibits angiogenesis has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Additionally, It is noted that a wherein clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited, MPEP 2111.04. Given that Healy et al. teach determining the in vitro kinase activity of an Axl polypeptide where the Axl polypeptide has kinase activity in the absence of the compound, (see Fig. 5 and page L1276, 2nd col.), performing a cell-based assay in an endothelial cell by contacting human pulmonary endothelial cells that express human Axl (see Fig. 2) with the Axl ligand Gas 6 and determining the effect of this interaction on cell number (see Abstract, p. 1276, left column, and Fig. 6), and assaying apoptosis in human endothelial cells expressing recombinant wild type Axl (see p. L1278 and Figure 9 and 10), the limitations of the claimed process steps are met. The claims do not limit the compound to be tested so, GAS-6 meets the limitations

of a compound. Based on the teachings of Healy et al. one of skill in the art would immediately envision that the desribed assays could be used for determining positive or negative effects of a compound on the endothelial cells and Axl activity.

Applicants further point out that claim 1 requires assaying in vitro kinase activity of an Axl polypeptide and performing a cell-based assay in an endothelial cell comprising said Axl polypeptide. In contrast, Healy et al. do not teach performing both of these assays in order to identify an inhibitor of angiogenesis. Thus, Healy et al. clearly does not anticipate claim 1 and its dependent claims.

Applicants' arguments have been considered, but have not been found persuasive because, as set forth above and previously, Healy et teach both ssaying in vitro kinase activity of an Axl polypeptide and performing a cell-based assay in an endothelial cell comprising said Axl polypeptide

Applicants argue that the Office states that "'determining the functional effects of the compound upon the kinase activity of the Axl polypeptide,' when given its broadest reasonable interpretation encompasses assaying cellular responses such as increases or decreases in cellular proliferation and apoptosis" (Office action, page 10, third paragraph). Applicants point out that this language ("determining the functional effect") is no longer present in claims 1 or 27. This language was removed from claim 1 in the amendment of October 5, 2007 and from claim 27 in the amendment of March 12, 2008. Further, Applicants assert that this is an unreasonably broad interpretation of claim 56. As discussed above, the specification defines "determining a functional effect," which includes assaying kinase activity. However, claim 56 does not recite "determining a functional effect." Claim 56 recites "determining a functional effect of the compound upon the kinase activity of the Axl polypeptide." This claim cannot reasonably be interpreted as including determination of any functional effect; a proper interpretation is determining the effect of a compound on the kinase activity of the Axl polypeptide. However, solely in the interest of expediting prosecution, claim 56 is amended herein to recite "assaying the kinase activity of the Axl polypeptide." Healy et al. teach only assaying the effect of Gas 6 on Axl kinase activity. As discussed above, Gas 6 is neither an inhibitor of Axl nor an inhibitor of angiogenesis. Thus, Healy et al. do not expressly or inherently teach a method of identifying a compound that is an inhibitor of angiogenesis and this reference does not anticipate the claims.

Applicants' arguments have been considered, but have not been found persuasive because, as set forth above, the preamble recitation of a method for identifying a compound that inhibits angiogeneis does not have patentable weight because the process steps are able to stand alone and Healy et al. teach the claimed process steps.

Claims 12, 15-18, 41-44, and 57-60 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Healy et al. (Am. J. of Physiology, Lung Cell Molecular Physiology, June, 2001 280: L1273-L1281, previously cited) as applied to claims 1, 14, 27, 54-56 and 61, above, in view of Varner and Cheresh (Current Opinion in Cell Biology, October 1996, 8:724-730, previously cited), in further view of Ruoslahti et al (US Patent 6,180,084 January, 2001, previously cited), in further view of Panzer et al. (United States Patent Application Publication No.: 2004/0048253, February 21, 2001, previously cited), and in further view of Klinghoffer et al. (United States Patent Application Publication No.: 2004/0077574, May 23, 2002).

Appplicants argue that in order to establish a primafacie case of obviousness, the Office must establish that (1) there is some suggestion or motivation to combine the references, either in the references or in common general knowledge of one of skill in the art (MPEP § 2143.01); and (2) there is a reasonable expectation of success (MPEP § 2143.02). In addition, the Office must show that the references teach or suggest all claim limitations. "When determining whether a claim is obvious, an Examiner must make 'a searching comparison of the claimed invention - including all its limitations - with the teaching of the prior art.' Thus, 'obviousness requires a suggestion of all limitations in a claim.'" Ex parte Mumper BPAI, Appeal No. 2008-2332, June 27, 2008. Claims 12, 15-18, 41-44, and 57-60 depend from claim 1, 27, or 56.

Appplicants argue that based on the discussion of Healy et al. above, Applicants maintain that Healy et al. do not teach all the limitations of the claims, namely that Healy et al. do not teach or even suggest identification of an inhibitor of angiogenesis. Further, Healy et al. make no suggestion that Axl polypeptide plays a role in angiogenesis. Rather, Healy et al. teach only that Axl and its ligand Gas 6 have anti-apoptotic activity in HPAEC cells and that this may be "relevant to endothelial cell survival in the quiescent environment of the vessel wall" (Healy et al., abstract).

Applicants argue that the Office action alleges that Varner and Cheresh teach a role for integrin alphaVbeta3 in angiogenesis. However, Varner and Cheresh do not teach or suggest a role for Axl polypeptide in angiogenesis nor selecting a compound that inhibits in vitro kinase activity of Axl polypeptide and inhibits angiogenesis phenotype in a cell-based assay to identify inhibitors of angiogenesis. Therefore, this reference does not cure the deficiencies of Healy et al. Likewise, Panzer et al. and Ruoslahti et al. teach only general methods of screening small molecules and other compounds for use in diagnosis or therapy. There is no discussion of Axl polypeptide in these references; therefore they cannot cure the deficiencies of Healy et al. Klinghoffer et al. teach only use of siRNAs for altering gene expression. This reference discloses Axl only as containing a potential protein tyrosine phosphatase 1B recognition motif (Klinghoffer et al., paragraph [0016]) and does not teach or suggest a role for Axl polypeptide in angiogenesis. Therefore Klinghoffer et al. cannot be used to cure the deficiencies of Healy et al.

Applicants argue that the Office does not provide any rationale for one of skill in the art to combine or modify the cited references. Taken together, one of skill might be motivated to assay regulation of apoptosis by Axl, not regulation of angiogenesis. However, the claims are based on the novel recognition that inhibition of Axl polypeptide inhibits angiogenesis. None of the cited references disclose that Axl has any role in angiogenesis, nor suggest that inhibitors of Axl could be inhibitors of angiogenesis. Without the recognition that inhibition of Axl inhibits angiogenesis, there is no motivation to combine the references and no expectation of success in arriving at the claimed invention by combining the references. Thus, alone or in combination, the cited references do not support a primafacie case of obviousness.
In sum, none of the references cited by the Office teach or suggest, either alone or in combination, all of the features of Applicants' claims. It remains well-settled law that obviousness requires at least a suggestion of all of the features in a claim. See Exparte Mumper

(BPAI, Appeal 2008-2332, June 27, 2008) citing CFMT, Inc. v. Yieldup Intern. Corp., 349 F.3d 1333, 1342 (Fed. Cir. 2003) and In re Royka, 490 F.2d 981,985 (CCPA 1974). The Office has not met this burden and has not provided any "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." KSR Int'l v. Teleflex, 127 S. Ct. 1727, 1741 (2007) (quoting In re Kahn, 441 F.3d 977,988 (Fed. Cir. 2006).

Applicants arguments have been considerd, but have not been found persuasive. First, as set forth above, Healy et al. teach the limitations of the process steps claimed in the base claims and the recitation of identifying an inhibitor of angiogenesis in the preamble is not given patentable weight for the reasons set forth above . One of skill in the art would immediately recognize that the study of viability and apoptosis of endothelial cells would be relevant to the study of angiogensis as endothelial cells growth would be required for the formation of additional blood vessels. In particular, Healy et al. state that apoptosis has a role in vascular remodling tumor angiogenesis and a balance between cell growth and death may be required for vascular remodeling, see page L1280- left col. Given the importance of endothelial growth to angiogenesis and vascular remodling and given the importance of these events to normal physiology and disease like tumorigenesis, and given the role shown for Axl activity in endothelial cell survival, one of skill in the art would be motivated to study the effects of various compounds such as an antibody, antisense molecule, RNAi, or small organic molecule taught by Panzer et al. , Ruoslahti et al , and Klinghoffer et al. in screens to identify compounds that affect Axl and endothelial cell survival. Additionally, given that Varner and Cheresh teach that integrin alphaVbeta3 is significantly upregulated on vascular cells within human tumors and in response to growth factors and plays a biological role in a critical event of blood vessel formation during tumor angiogenesis, it would be obvious to one of skill in the art to assay the effect that the applied compounds have on alphaVbeta3 expression in conjunction with their effects on Axl kinase activity and cell survival and apoptosis.